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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,887	07/03/2001	Raghavan Rajagopalan	MRD-61	2188

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/898,887	RAJAGOPALAN ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed 6/24/04, claim 15 has been amended. Claims 15-46 remain pending.

Applicants' arguments filed 6/24/04 have been considered and found not persuasive.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of performing a "phototherapeutic procedure". The term "therapy" (or phototherapy) implies an assertion that an ill patient can be treated such that manifestations of the illness are ameliorated. However, there is no evidence that this will happen in the instant case. If one takes a "drug" that has been shown to be effective in one way or another, and subsequently endeavors to create a "prodrug" thereof, "unpredictable" effects *in vivo* can result. Consider the following:

- Shabat D. (*Proceedings of the National Academy of Sciences* **98** (13) 7528-33, 2001)

discloses a prodrug that is not activated by endogenous enzymes. This supports the conclusion of "unpredictability" in that the instantly claimed compounds may not be activated by endogenous enzymes.

- Smal (*Biochemical Pharmacology* **49** (4) 567-74, 1995) discloses (e.g., p. 572) that 2-Leu-MTX is unsuitable as a prodrug

- Saboulard (*Molecular Pharmacology* **56** (4) 693-704, 1999) discloses (e.g., page 701, col 1) that prodrugs of AZT are not effective.

- Jaffar (*Bioorganic and Medicinal Chemistry Letters* **9** (1) 113-8, 1999) discloses (e.g., table 1) prodrugs of aspirin that are not effective.

- Deverre J. R. (*Pharmaceutica Acta Helvetiae* **67** (12) 349-52, 1992) prepared a prodrug, and discovered inactivity of the prodrug *in vivo*, either by the oral route (10 mM) or after an intraperitoneal administration (1 mM).

- Miyauchi M (*Chemical and Pharmaceutical Bulletin* **38** (7) 1906-10, 1990) discloses an attempt to produce orally bioavailable prodrugs of 3-thiazoliomethyl cephalosporin (compound number 1) Lipophilicity of the resulting derivatives (8-10) was suitable for passive absorption from the intestinal tract, and chemical stability in phosphate buffer solution (pH 6.86) was moderate. However, when administered orally to mice, these derivatives were mainly transformed to a novel 3-spiro cephalosporin 11, and desired reconversion to the 3-thiazoliomethyl cephalosporin was minor. These results showed that the derivatives (8-10) tested in this study did not serve as orally active prodrugs of 3-thiazoliomethyl cephalosporin 1.

- Hadad S (*Journal of Pharmaceutical Sciences*, **81** (10) 1047-50, 1992) examined the pharmacokinetics and efficacy of five monoester prodrugs of valproic acid (VPA). Valproic acid an anti-epileptic drug. Four of the five prodrugs were ineffective in mitigating symptoms of epilepsy. In addition, a pharmacokinetic- pharmacodynamic correlation was absent in the case of B-VPA and H-VPA.

- Langer (*J. Med. Chem.* **44**, 1341-1348, 2001) has examined the effects of bonding a peptide, via a linker, to daunorubicin and doxorubicin. As stated (p. 1344, col 1, paragraph 3, attaching a peptide to the amino group of daunorubicin or doxorubicin eliminated activity.

- Mamber S. W. (*Journal of Pharmacology and Experimental Therapeutics* **274** (2) 877-883, 1995) discloses prodrugs of taxol. The 2'- and 7- phosphate analogs BMY46366 and BMY46489 were ineffective as prodrugs.

- Niemi (*J. Med. Chem.* **42**, 5053, 1999) prepared compounds which were intended to be prodrugs of clodronic acid. As it happened, benzoyloxyproyl esters of clodronic acid were ineffective as prodrugs.

None of the foregoing references pertain to photodynamic therapy specifically. However, consider the following:

- Hillemanns, P. (*International journal of cancer. Journal international du cancer*, 81 (1) 34-8, 1999) discloses that photodynamic therapy is not effective to treat cervical intraepithelial neoplasia

- Li W. (*Journal of photochemistry and photobiology. B, Biology* 60 (2-3) 79-86, 2001) discloses that photodynamic therapy is not effective when applied to K562 cells.

- Anderson Gregory S (*Journal of photochemistry and photobiology. B, Biology* 68, (2-3) 101-8, 2002) discloses that solid tumor cells are refractory to photodynamic therapy.

- Grossweiner L. I. (*Photochemistry and photobiology* **46** (5) 911-7, 1987) discloses (table 4, page 916) that photodynamic therapy was not effective when administered to a male patient with a tumor located in the anterior tonsillar pillar.

- Pope A.J. (*Journal of urology* 145 (5) 1064-70, 1991) discloses (e.g., page 1068, col 2) that photodynamic therapy is not effective with subjects afflicted with invasive tumors.

- Gluckman J. L. (*Laryngoscope* 101 (1 Pt 1) 36-42, 1991) discloses that photodynamic therapy was not effective in several patients with advanced head and neck cancer.

Clearly, if one takes a compound which has been shown to be therapeutically effective, and attaches a group or substitutent to it, the result is often loss of activity. Thus, one cannot "predict" therapeutic efficacy of a prodrug on the basis of efficacy of the "parent" drug. This is true whether the patient is being exposed to light or not. In addition, as is evident from the references, attempts to perform a phototherapeutic procedure lead to "unpredictable" results.

Accordingly, in view of the unpredictability of the art, the absence of any working examples, the absence of any guidance as to which compounds will be effective, and the state of the art, it is fair to conclude that "undue experimentation" would be required to perform a phototherapeutic procedure on an ill patient, given that the term "therapeutic" means that symptoms of the disease will be ameliorated.

A matter separate from the foregoing, is that applicants have not shown that the compounds (to which the claims are directed) are effective as photosensitizers, even *in vitro*. One cannot predict the propensity of a compound to act as a photosensitizer merely by viewing its structure. This issue is of significance because, *to the extent* that photodynamic therapy has proven effective in the past, efficacy has been dependent on the ability of the compounds to act as photosensitizers. In the presence of light, photosensitizers facilitate the transfer of energy to oxygen, resulting in the production of singlet oxygen. The presence of singlet oxygen leads to a variety of effects *in vivo*, including damage to cell membranes,

vascular injury and coagulation. "Downstream" from this is neutrophil activation, platelet activation, and production of prostaglandins and thromboxane. However, applicants have not shown that the disclosed compounds function as photosensitizers, or that they can facilitate the production of singlet oxygen.

In response to the foregoing, applicants have made two statements that appear to be inconsistent. On page 17 (of 20), it is asserted that the claimed sulfenate can be used to treat cancer; on page 18 (of 20), it is asserted that the claimed sulfenate is not a drug. If the claimed sulfenate is indeed effective to treat cancer, then it is a drug. Accordingly, it is not apparent which of the two statements controls.

Applicants have also argued that the claimed compounds cause cellular injury by a "type I" mechanism, rather than a "type II". And as asserted in the declaration, homolytic scission of the sulfur-oxygen bond will occur, generating free radicals. It may be the case that such radicals will be generated. But this does not necessarily mean that "direct energy or electron transfer from the photosensitizer to the cellular components" will occur. Applicants have provided no reason or explanation as to why an oxygen-centered or thiyl radical will transfer energy to a cellular component, and no such reason is evident. As for electron transfer, it is more likely that this will occur in the opposite direction from that intended. An oxygen-centered radical is much more likely to abstract a hydrogen atom

(i.e., a hydrogen radical) from a "cellular component" than it is to donate an electron (to the same). This is not to say, however, that such oxygen-centered or thiyl radicals will not cause tissue damage. One of the points to be made is that if applicants are going to assert that the compounds are acting by a "type I" mechanism, it would behoove applicants to explain why it is that the skilled photochemist would believe that the claimed sulfenates are acting by a mechanism that is substantially the same as another agent which has been shown to be therapeutically effective. It is noted that anthracycline is mentioned on page 6 (line 3) of the specification. Applicants have stopped short, however, of even asserting that their compounds act by the same mechanism as anthracycline. In the event that applicants are able to present evidence and/or arguments which indicate that the efficacy of anthracycline derives solely from homolytic bond cleavage, the "prodrug" references above will still be relevant. The point of many (although not all) of these references is that if one takes a drug which has been shown to be pharmacologically effective (with respect to one disease or another), and attaches another group to it, elimination of efficacy is frequently the result.

Applicants have also questioned the examiner's assertion that the term "therapy" implies that the manifestations of an illness are ameliorated, and have suggested that perhaps the examiner's understanding of this term is at odds with that of the skilled medical practitioner. It is suggested that applicants consult a medical dictionary for a discussion of this term.

After this, applicants may present arguments as to why the skilled medical practitioner would regard the term "therapy" as meaning that the ill patient would derive no benefit from the efforts of the medical practitioner to achieve the same.

As a hypothetical matter, suppose that applicants could demonstrate that proliferation of glioblastoma cells, implanted in a rat, could be substantially reduced. Even this evidence would not justify a claim drawn to performing a "phototherapeutic procedure"; this term would mean that virtually any disease could be successfully treated, which would not be demonstrated by the glioblastoma example.

The rejection is maintained.

✧

Claims 15-46 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 15 recites "effective amount". Suppose that the "effective amount" in a given patient is "X" micrograms. Suppose further that, in a given experiment, only 0.7 X micrograms is administered to the target tissue. What would be the manifestations of this experiment that would distinguish it from the experiment in which "X" micrograms was administered?

- Claim 29 recites that "E is associated" with one of the recited biomolecules. What is meant by this? Does this mean that "E" must be present as a complex with one of the recited biomolecules at the time of administration, or does it mean that when "E" is administered (unattached to the sulfenate) to a mammal, that "E" forms a non-covalent association with one of the biomolecules, or is something else intended? What is meant by the assertion that (e.g.) a somatostatin receptor binding molecule is

"associated" with a polyol, or that a steroid receptor binding molecule is "associated" with a nucleoside?

- Claim 29 recites that "E" can be "associated" with a dendrimer. One interpretation of this embodiment is that the claimed sulfenate compound is not administered as such, but rather is administered as a conjugate of the dendrimer, such that "E" is bonded to an erstwhile nucleophilic group on the dendrimer. If this is the intention, claim 29 should be written in independent form, and the claim made clear that a conjugate is intended.

- Several of the claims (e.g., claims 30-33, 40, 41, 43) recite the qualifier "about" in reference to a range, e.g, "about 0.1 mg/kg to about 500 mg/kg". However, this renders the claims indefinite as to the upper and lower limits on the range. It is suggested that "about" be deleted at every occurrence.

- Claims 32-36 and 42-46 imply that the sulfenate is being administered as a composition. However, the independent claims (on which they depend) do not suggest or imply that the sulfenate is administered in this way. Accordingly, the claim dependence is improper. It is suggested that claims 32-36 and 42-46 be written in independent form.

- The claims are drawn to a method of performing a "phototherapeutic procedure". The claims are indefinite as to what the objectives might be, and what the manifestations of a successfully completed procedure might be. In response, applicants have argued that the mere adminstration of the compound, and exposure to light constitutes a "phototherapeutic procedure" in and of itself. The examiner disagrees. Consider the following example:

A method of performing a therapeutic procedure comprising the step of administering 20 mL of water to a subject orally.

One could argue that, at least in one sense, this hypothetical claim meets the requirements of §112 second paragraph. Certainly, it is clear to one having no skill in science or medicine what the procedure is for drinking a glass of water. What is not clear (in this example) is what therapeutic objective is being pursued, or how one is trying to achieve that objective. Returning to the issue of

phototherapy, consider the following hypothetical claims:

100. A method of producing an oxygen-centered radical and/or a thiyl radical within a target tissue of an animal, said method comprising

(a) administering to the target tissue a sulfenate compound having the formula ... [etc.]

(b) exposing said target tissue with light ..... with sufficient power and fluence rate to produce said oxygen centered and/or thiyl radical.

101. A method of treating cancer comprising

(a) administering to a patient in need thereof a sulfenate compound having the formula ... [etc.] and

(b) exposing said target tissue with light ..... for a time and under conditions effective to inhibit proliferation of tumor cells.

The examiner makes no representation that either of claims 100 or 101 would be allowable. The purpose of the claims is to illustrate that it is possible to recite an objective, and a means of achieving that objective, such that both are clear and definite. As matters currently stand, however, claim 15 remains indefinite as to what the objectives might be, and what the manifestations of a successfully completed procedure might be

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800